Game Plan for Therapeutic Cancer Vaccines

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Types of Therapeutic Anti-Cancer Vaccines

Vaccine Type			
Whole Cell Vaccines		Antigen/Adjuvant Vaccines	Viral Vector / DNA-based Vaccines
Autologous	Allogeneic	GM2 ganglioside vaccine combined with the QS-21 adjuvant (GMK)	plasmid DNA vaccine expressing the Melan-A/MART antigen
Dendritic Cell Vaccines	CanVaxin™, irradiated allogeneic melanoma cell line plus BCG)	Effective, but inferior to high-dose IFN (another immunotherapy) in Phase III trial	Melan-A/MART-1 specific T cell responses were evident by ELISPOT, but no HBsAg-specific antibodies detected
Provenge (sipuleucel-T), is the first approved cell-based vaccine			

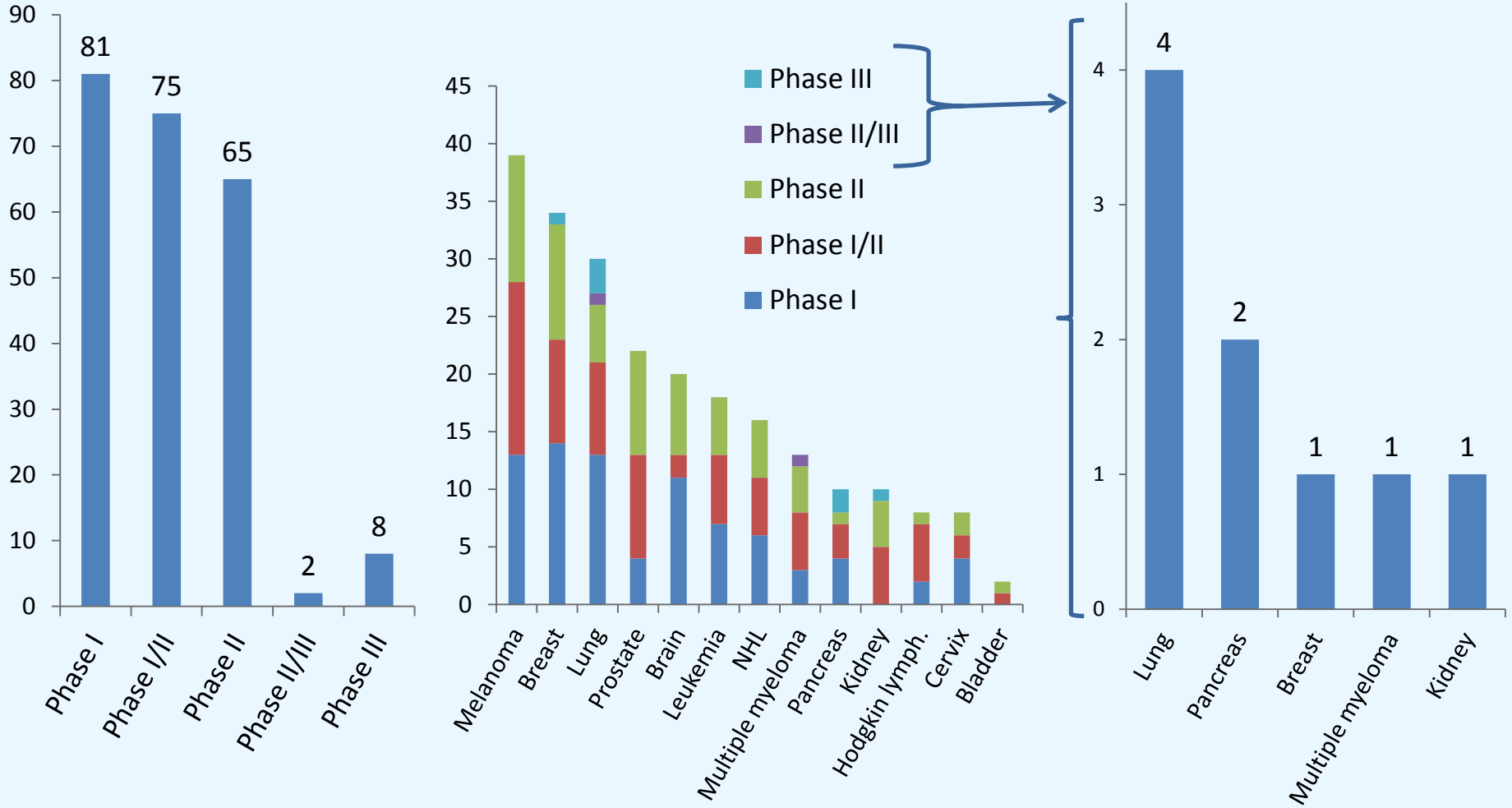
Trends in Cancer Vaccine Development & Lessons Learned

Status of Cancer Vaccine Research

~230 vaccines are in clinical development

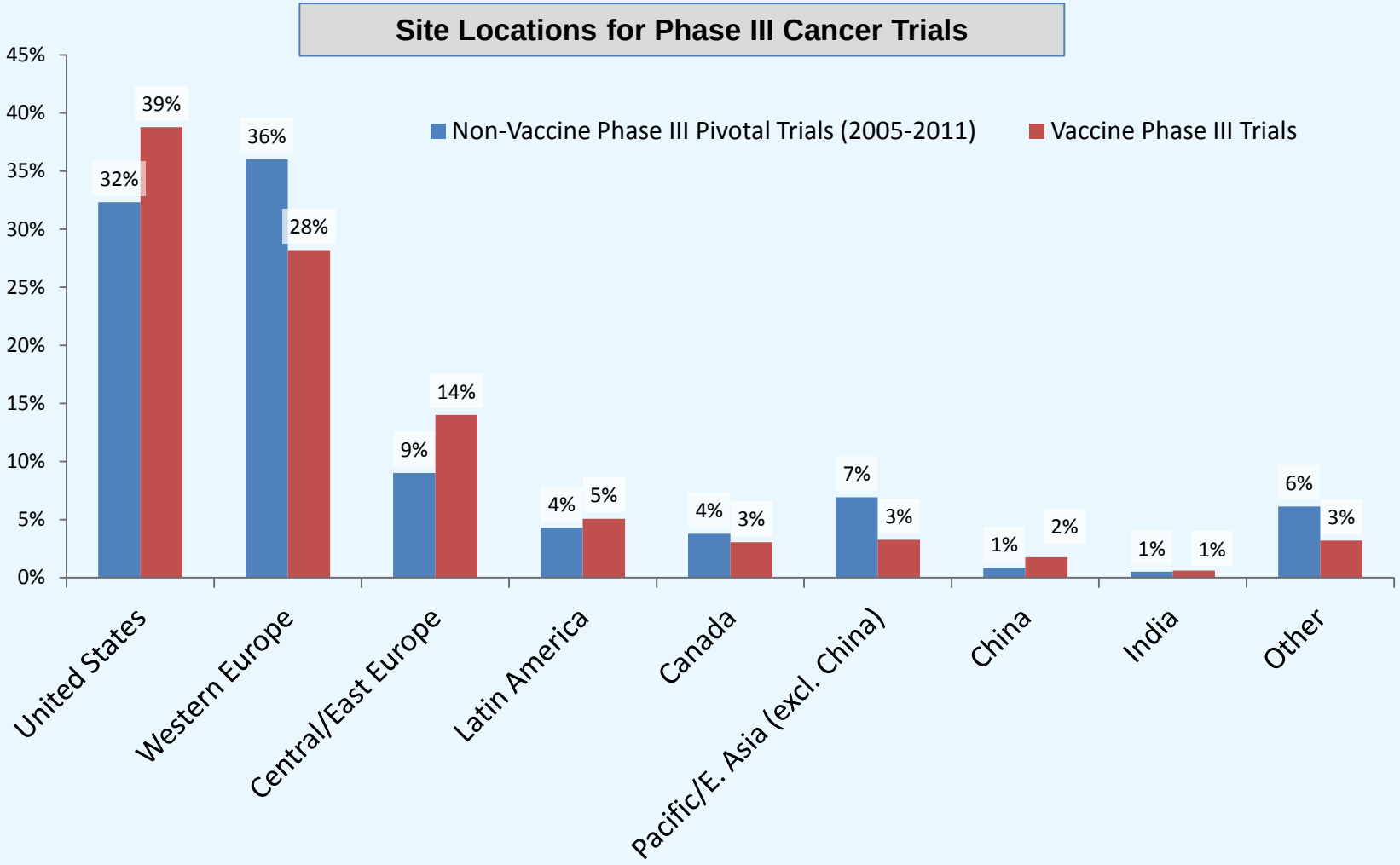
Melanoma, breast, and lung have the highest overall activity

Lung cancer has more late-stage candidates



Source: Dayoub, E., Davis, MM. Relationship of therapeutic cancer vaccine development to population disease burden and five-year survival. Human Vaccines Nov 2011; Data H1 2011

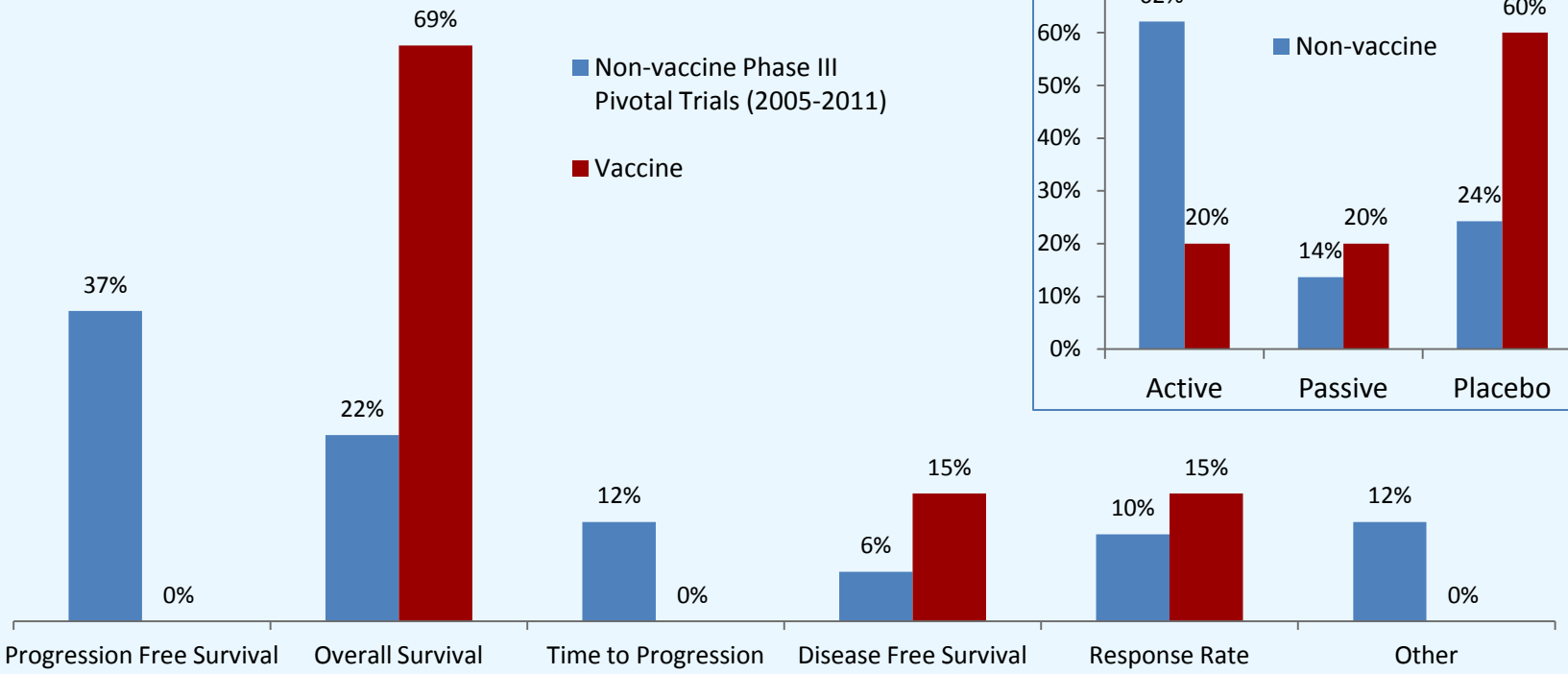
Geography of Cancer Vaccine Research



Sources: Pivotal trial data from *Oncology Clinical Trials: The Roadmap to FDA Approval*. VOI Consulting / insiteinvestigator database; Vaccine trial locations from clinicaltrials.gov and published articles on Phase III trials

Trial Design

PRIMARY ENDPOINT
Vaccine trials are much more likely than other cancer studies to feature overall survival as a primary endpoint:



COMPARISON ARM
Placebo controls are also much more common:

RANDOMIZATION
Vaccine trials also tend to overweight the investigative arm: ~75% of Phase III studies have 2:1 randomization as compared to >10% of non-vaccine pivotal cancer trials.

Sources: Pivotal trial data from *Oncology Clinical Trials: The Roadmap to FDA Approval*. VOI Consulting / insiteinvestigator database; Vaccine trial data from clinicaltrials.gov and published sources. Passive controls can take the form of comparisons to best supportive care or the lack of investigational drug in the comparison arm.

CLINIPACE WORLDWIDE

Trial Size

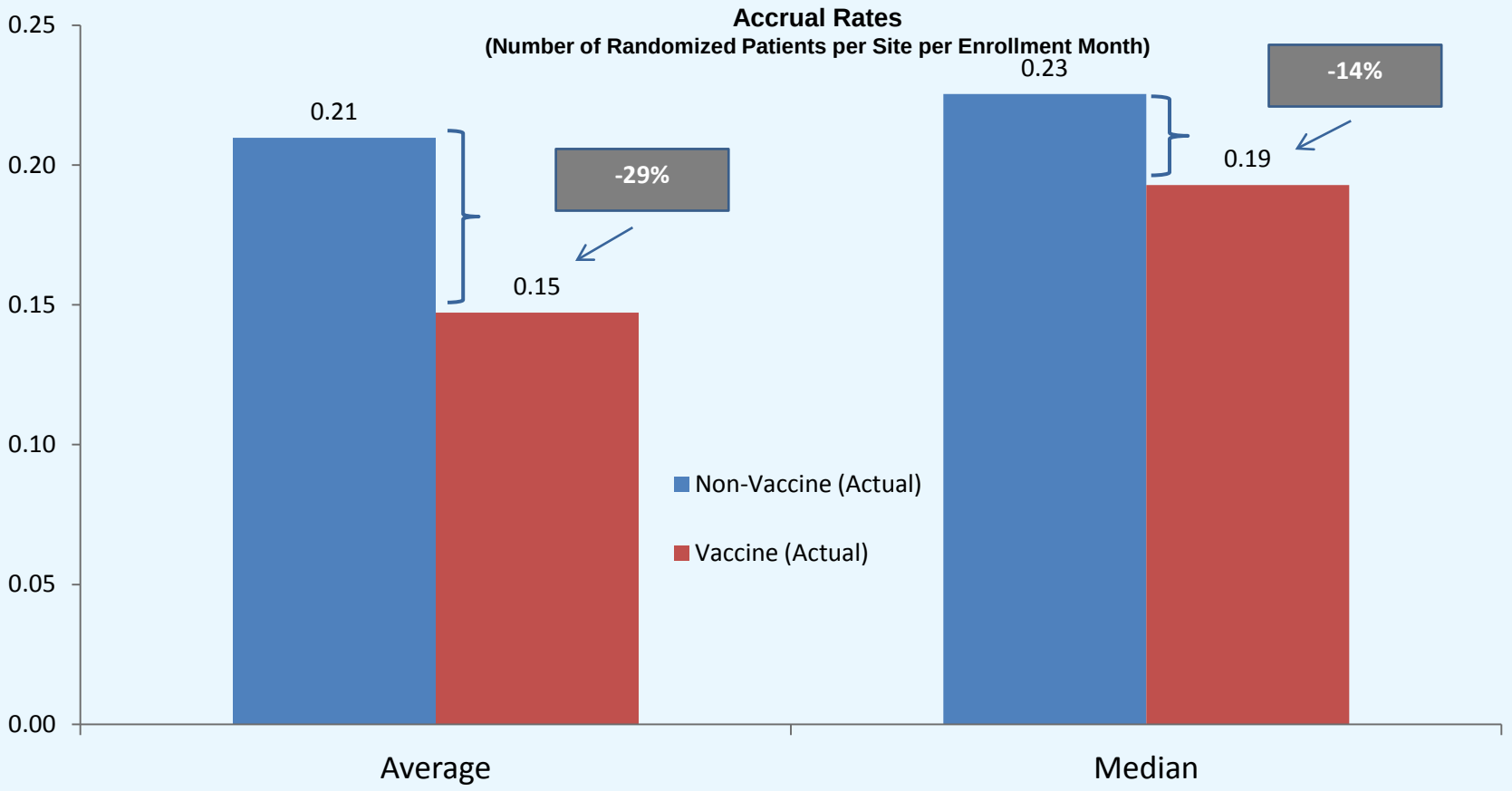
Cancer vaccine trials, on average, are smaller than Phase III pivotal trials for other cancer drugs. However, cancer vaccine trials currently underway are very similar in terms of # of patient & sites.

Parameter	Phase III Trial Type	Average	Median	Min	Max
Number Patients	Non-Vaccine (Actual)	667	571	100	3387
	Vaccine (Actual)	256	177	98	512
	Vaccines (Projected)	687	568	230	1476
Number of Sites	Non-Vaccine (Actual)	106	88	19	476
	Vaccine (Actual)	40	27	17	75
	Vaccines (Projected)	108	76	10	295

Sources: Actual trial data from *Oncology Clinical Trials: The Roadmap to FDA Approval*. VOI Consulting / insiteinvestigator database; Projected vaccine trials data from clinicaltrials.gov.

Randomization Rates

To date, Phase III cancer vaccine trials have experienced substantially lower randomization rates. This problem has led to a discontinuation of at least one trial (i.e. BiovaxID had a 563 patient target but enrolled only 234 after ~8 years).

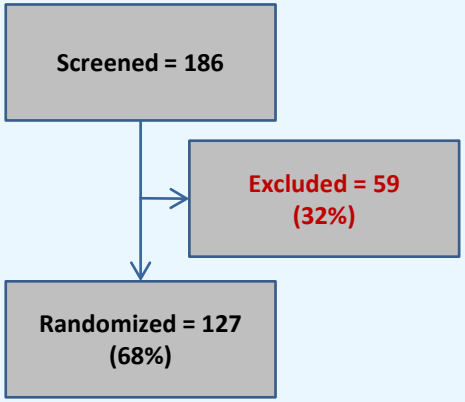


Sources: *Oncology Clinical Trials: The Roadmap to FDA Approval*. VOI Consulting / insiteinvestigator database. BiovaxID information from Schuster, S. Vaccination With Patient-Specific Tumor-Derived Antigen in First Remission Improves Disease-Free Survival in Follicular Lymphoma. Journal of Clinical Oncology Jul 10 2011

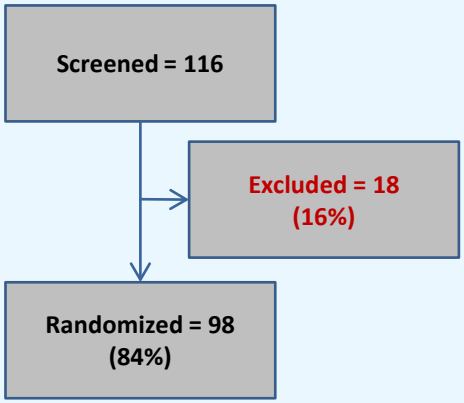
Screening Rates

Slow accrual may be due in part to high screen failure rates for vaccine trials (average = 29% as compared to <20% for pivotal trials of other cancer drugs).

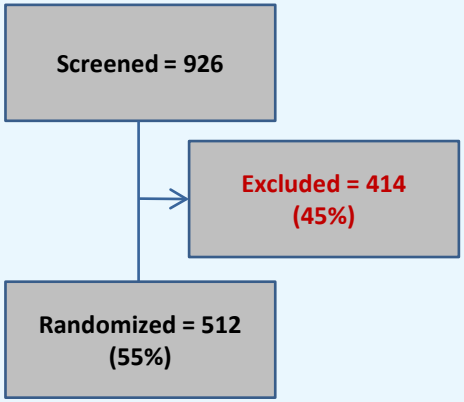
Provenge (D9901)



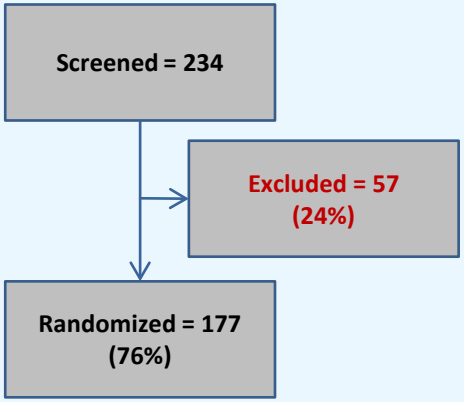
Provenge (D9902A)



Provenge (D9902B)



BiovaxID



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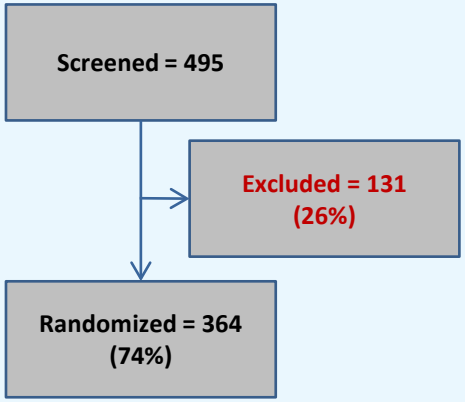


Source: *Oncology Clinical Trials: The Roadmap to FDA Approval*. VOI Consulting / insiteinvestigator database

Cancer Vaccine Development Lessons Learned

- In comparison to the design and execution of other types of cancer trials, vaccine studies show more similarities than differences (e.g. number patients, number sites, locations).
- Nonetheless, there are important differences:
  - Overall survival strongly preferred as primary endpoint.
  - Placebo controls and 2:1 randomization are the norm.
  - Expect high screen failure and slower randomization rates.
  - Fewer sites with vaccine experience ➔ particularly in developing markets (with the exception of Central/Eastern Europe).
  - Expect strict regulatory scrutiny regarding efficacy and labeling that reflects the studied population.

Regulatory Strategy

FDA Regulatory Framework

- Regulated by FDA's Center for Biologics Evaluation and Research
- Reviewed by Office of Cellular, Tissue and Gene Therapy (CBER)
  - CDER and CDRH may be involved in product review
- Investigational New Drug (IND) application required for clinical trials in humans. FDA strongly recommends a pre-IND meeting to discuss study design, CMC and nonclinical (toxicology) plans
- Biologics License Application (BLA) required for marketing approval
- In parallel, device approval may be required for delivery device, companion diagnostic

Regulatory Challenges

- CMC can be very difficult
- Patient selection
- Conventional dose-escalation to reach MTD not relevant
- Use of adjuvants, companion diagnostic, delivery device
- Clinical response is often delayed
- Need to develop standardized assays
- Importance of placebo vs. active comparator group
- Standard clinically meaningful endpoint may not be relevant

Regulatory Considerations {EU vs. USA}

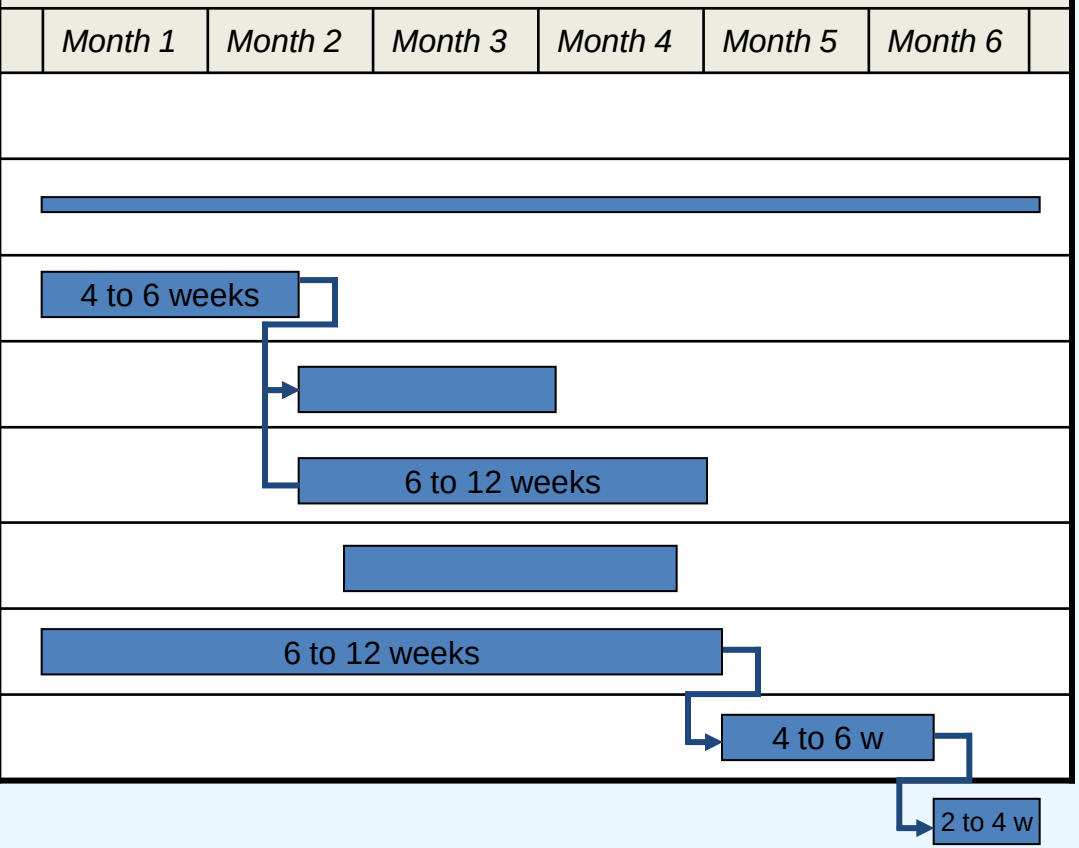
Overview of ATMPs

- European Legislation differentiates between Small Molecule Entities (SMPs) and Advanced Therapy Medicinal Products (ATMPs)
- Different Competent Authority (CA) and Ethics Committee (EC) approval timelines
- Separate GCP Guidelines for ATMPs

EU Study Start-up Timeline

Through the EMEA, there is a common framework for initiating clinical trials in EU Member States.

ID	Task name	Duration
1	Total elapsed time	24W
2	Compilation of submission	5W
3	Competent Authority	5W
4	Ethics Committee	10W
5	Site-specific assessment	8W
6	CTA negotiations	16W
7	R&D (UK only)	5W
8	Importation & Initiation	3W



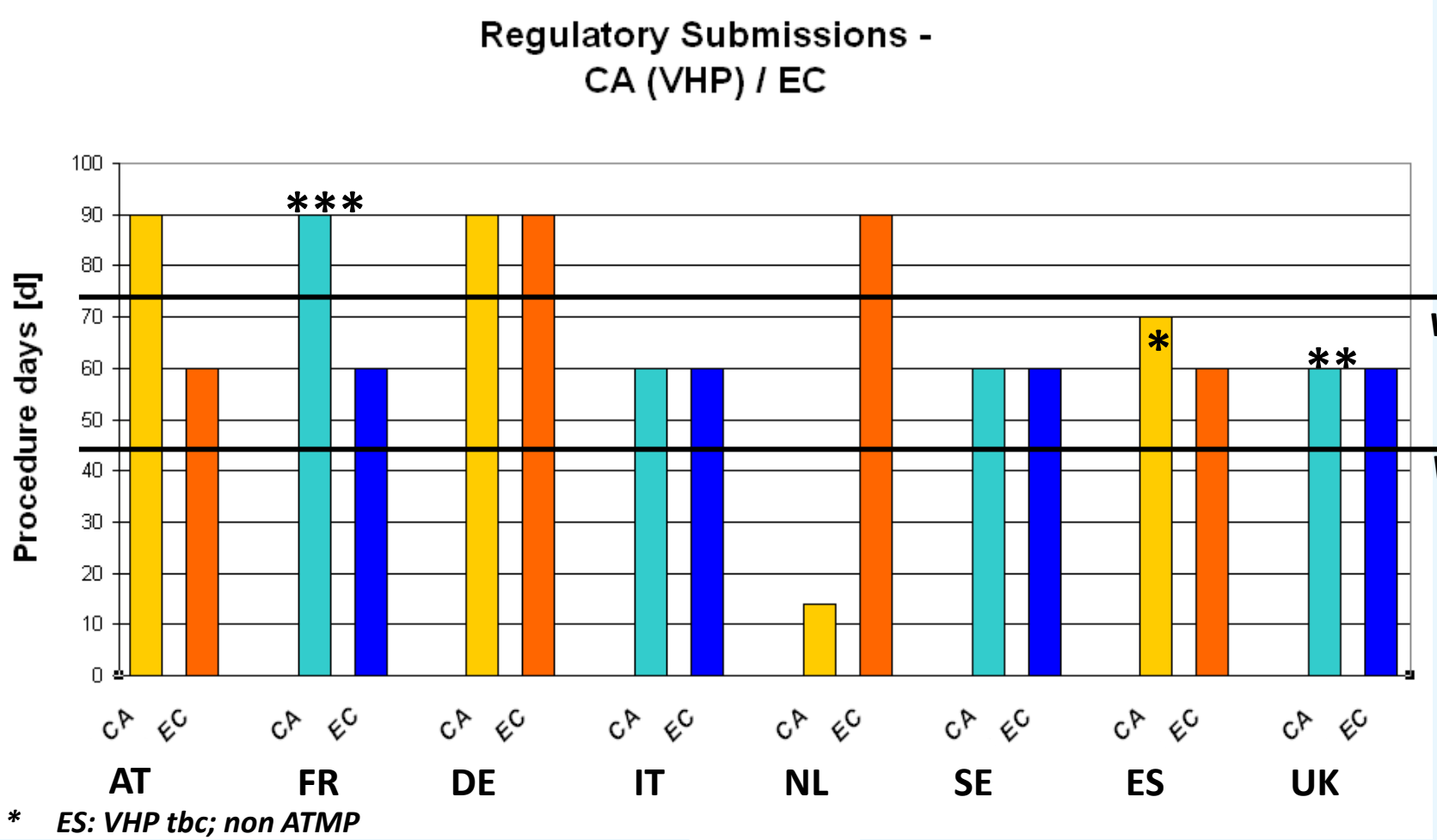
Voluntary Harmonisation Procedure

Voluntary Harmonization Procedure

- Launched as a EU pilot project in February 2009
- Amended guidelines issued in March 2010
- Facilitates multinational Competant Authority (CA) submissions across the EU
- A coordinated assessment of an application for a clinical trial
- The trial must still be authorized at national level
- Consists of 3 phases
- Centralized assessment but not centralized approval
- MINIMUM TIMELINE: 45 DAYS
- MAXIMUM TIMELINE: 75 DAYS*

* IF ASSESSMENT OF LOCAL DOCUMENTATION IS SATISFACTORY

Expected Approval Timelines ATMP



* ES: VHP tbc; non ATMP

** UK: 30 to 60 days

*** FR: 60 to 90 days

CLINIPACE WORLDWIDE

Clinical Development

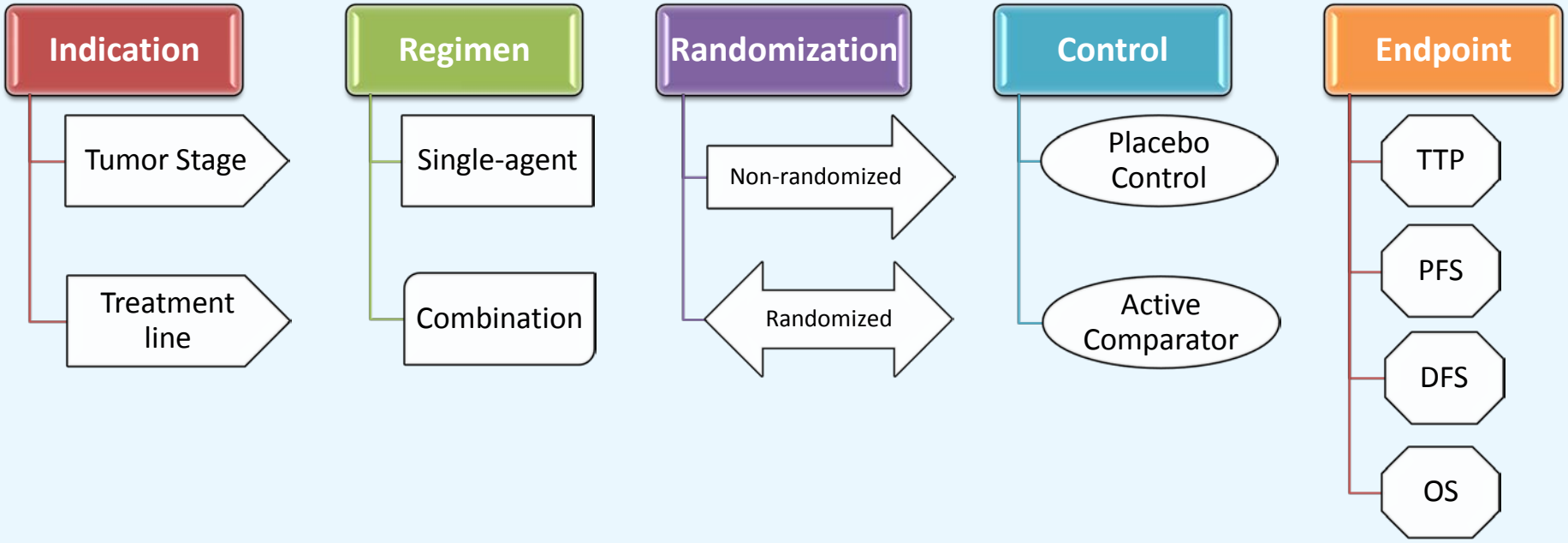
Selection of Tumor

Tumor Selection

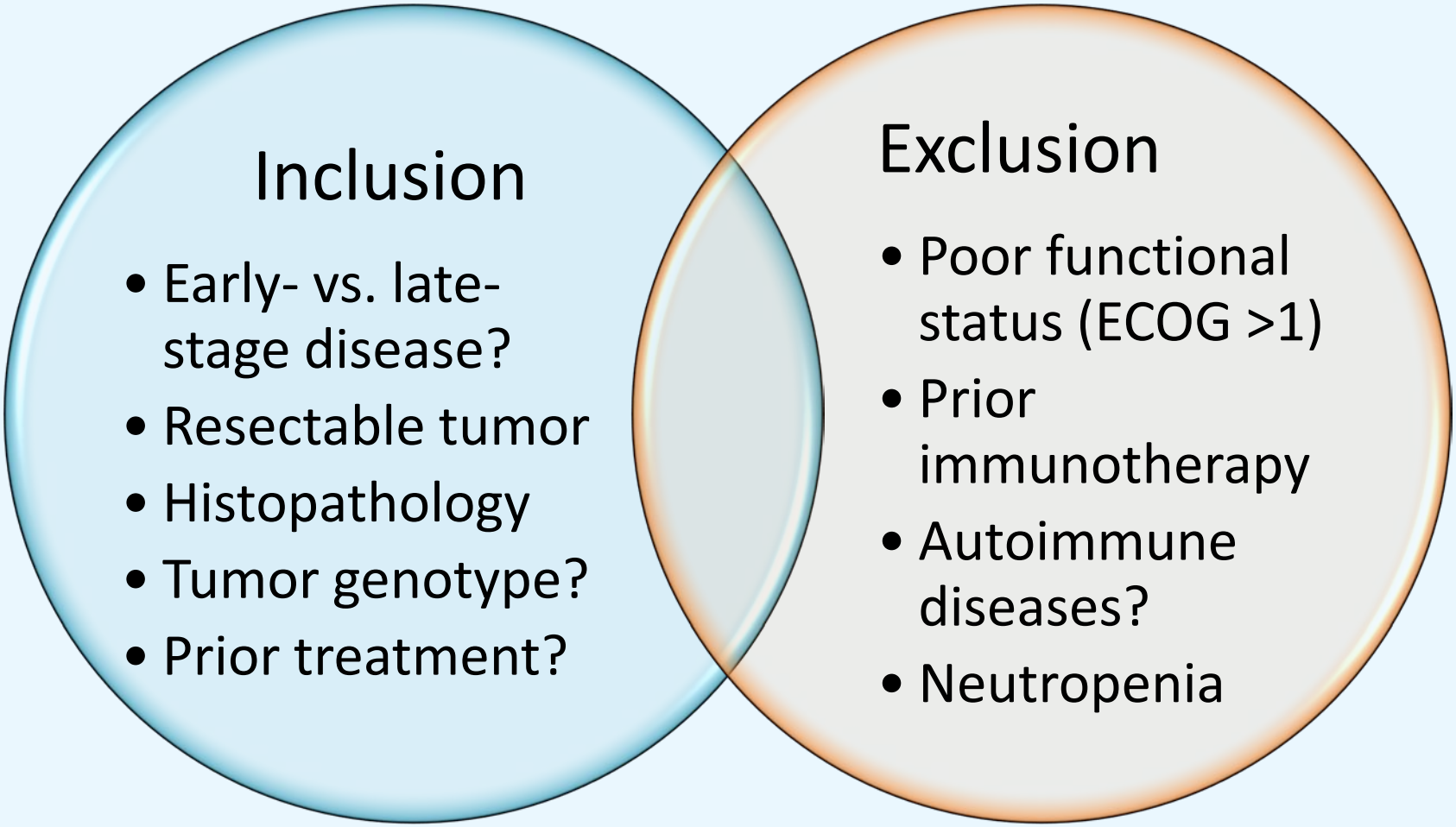
Many Types with Known Responsiveness to Immunotherapies

Solid Tumors	Hematologic tumors
Melanoma: IFN, IL-2, autologous LAK/TIL, anti-CTLA-4 (Yervoy) Renal cell : IL-2, autologous LAK/TIL Colon cancer: Levamisole Bladder cancer: BCG	NHL/CLL: Rituxan CML: Interferon alpha

Key Study Design Issues



Definition of the Patient Population



Randomized Trials in Phase II

Design Phase 3 Study

- Select measurable and clinically meaningful endpoint
- Define a clinically relevant risk
- Determine number of events based on 90% power

Design Phase 2b Screening Study

- Randomized, controlled design using the phase 3 study endpoint
- Determine number of events (approximately 25% of phase III)
- Determine threshold for phase 2 success, e.g. RR = 0.82

Conduct Phase 2b Screening Study

- Pre-determine decision-making criteria, e.g.
  - Observed RR > 0.82 → "no go"
  - Observed RR between 0.71 and 0.82 → further evaluation required
  - Observed RR < 0.71 → "clear signal, green light phase 3

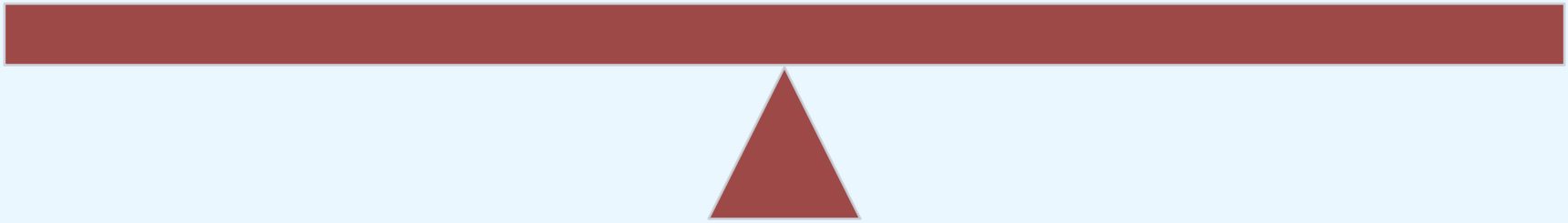
Endpoint Selection

Overall Survival

- Rapid disease progression of pivotal study
- Requires less frequent subject visits meaning less complicated and costly studies
- Requires longer duration studies than PFS and other endpoints based on tumor size or progression
- In a pivotal study, OS provides a stronger basis for approval than PFS or TTP

PFS/TTP/DFS

- Faster trial, especially good for slow disease progression or POC studies
- Imaging becomes pivotal thus greater cost associated with IAC, independent reads, and image management
- Imaging more frequent than SOC which means more expense and complexity for sites
- Immune recruitment to tumor sites can appear as progression under RECIST 1.1



Feasibility & Site Selection

Country Selection

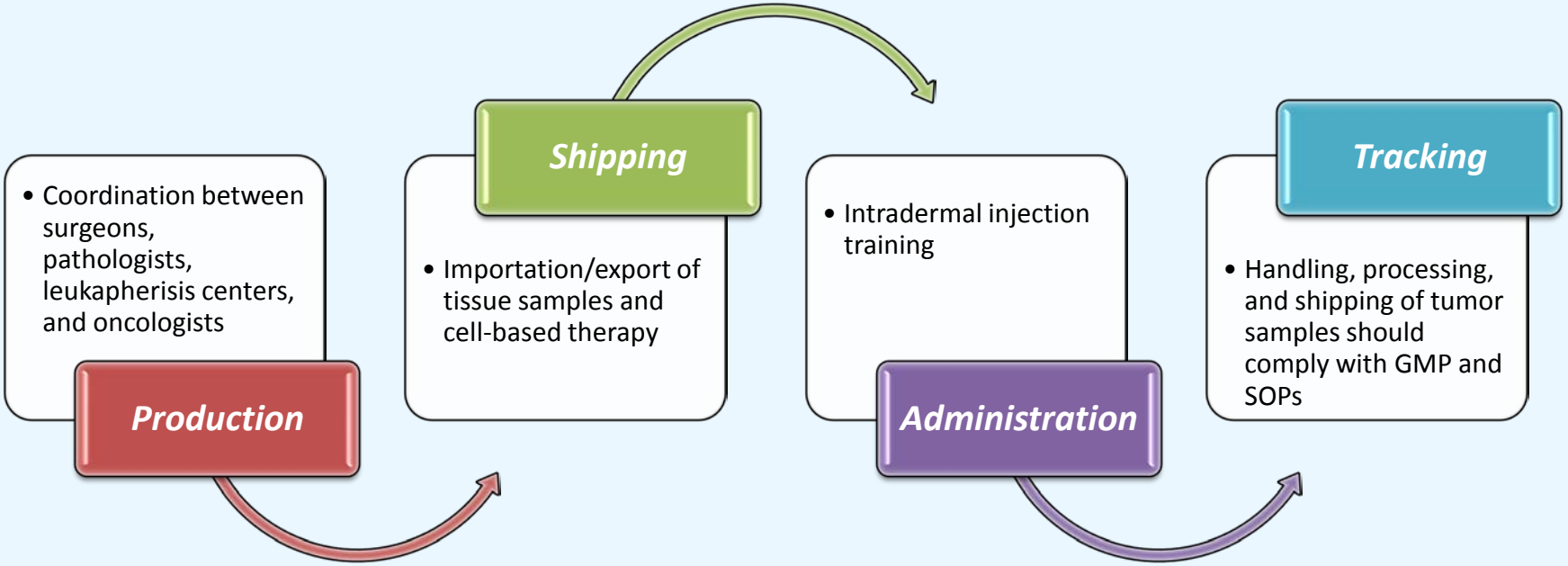
- Country selection based on a robust feasibility will provide the best chance of success for a trial where there is little precedent in most countries for anti-cancer vaccines
- Regulators outside the US may be unfamiliar and thus slower to approve trials with cell-based immunotherapy
- Exportation of tissue samples for vaccine production is highly regulated in certain countries
- Importation and customs delays can put vaccine shipments at risk
- Concentrating sites in emerging markets will hurt uptake at product launch because the complex nature of anti-cancer vaccines means that prescribers need significant experience during clinical trials to establish commercial use

Site Selection

- Site selection can include identification and evaluation of surgeons, pathologists, leukapherisis centers, and medical oncologist
- Site-specific capabilities and regulations, e.g. dedicated glove box for adjuvants, e.g. BCG
- OS trials following a series of inoculations tend to be easy for sites, opening up the possibility of community-based oncologists (e.g. CCOP) and central IRB sites

Logistics, Operations, and CMC

Logistical and Operation Issues for Autologous Cell-Based Vaccines



Chemistry, Manufacturing and Controls

Autologous product

- Culture period < 1 wk
- <20 final product vials/lot
- No cryopreservation

Bulk

Not performed

Final Release

-Gram stain and LAL
  -Pre-release
-Sterility
  -2 d read, pre-release
  -Final read, post-release

Allogeneic product

- Extensive culture period
- ~100 final product vials/lot
- Cryopreservation used

Bulk

-Sterility and LAL
  -Hold lot until all results available

Final Release

-Gram stain and LAL
  -Results pre-release
-Sterility
  -Results post-release

Chemistry, Manufacturing and Controls

Sterility Testing Failures

- Must define actions in procedures – including notifications, investigation, etc.
- Must perform susceptibility testing and report results to clinician

LAL Testing: False positives / Interference

- (1,3)-β-D glucan molecules; Found in cell walls of most yeasts, molds, culture media, cellulose filters, gloves, and uniforms
- High rates of invalid tests due to interference

Aseptic Processing: Media Fills

- Recommend completing in support of Phase II and later (earlier if high risk manipulations required)

FDA Guidance

- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines; Availability
  - http://www.federalregister.gov/articles/2011/11/07/2011-28726/guidance-for-industry-clinical-considerations-for-therapeutic-cancer-vaccines-availability

- Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf

Thank You

Questions & Answers

- Please submit your questions via the Q&A box on the left side of your screen

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